REMARKS

Status of the Claims

Claim 35 is amended to correct a minor typographical error. No new matter is introduced by this amendment.

Objection to claim 35

The Examiner objects to claim 35 as containing a typographical error. Claim 35 has been amended to correct this error. This objection may be withdrawn.

Rejection of claims under 35 U.S.C. § 103(a)

Claims 22, 24-29, and 31-39 stand rejected under 35 U.S.C. 103(a) as allegedly being obvious over Roth et al. (US Patent 5,747,469) in view of any one of Lu et al. (Cancer Res. 62: 1305-1310, 2002), Tango et al. (Hum. Gene Ther. 13: 1373-1382, 2002), or DePinho (US Patent 6,613,750), Tiemann (WO 01/11063) and Dirks et al. (US Patent 6,060,273). Applicants respectfully traverse this rejection.

An invention is unpatentable as obvious if the differences between the patented subject matter and the prior art would have been obvious at the time of invention to a person of ordinary skill in the art. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)). Thus, in order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. The proper analysis when determining obviousness includes consideration of the scope and content of the prior art; the level of ordinary skill in the prior art; the differences between the claimed invention and the prior art; and objective evidence of nonobviousness.

The Examiner has fallen into the trap of a hindsight analysis by relying on the general skill in the art to provide the missing claim elements and the requisite motivation to modify the methods of Roth et al., Lu et al., Tango et al., and Tiemann. However, the Federal Circuit has repeated held that the general skill in the art cannot "act as a bridge over gaps in substantive presentation of an obviousness case..." Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 1324, 50 USPQ2d 1161 (Fed. Cir. 1999 (citing Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991)). The mere fact that the combination or modification is technically within the capability of the artisan, or utilizes a known scientific principle, does not render the modification in question obvious. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1053, 5 USPQ2d 1434 (Fed. Cir. 1988 (citing Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 489 (Fed. Cir. 1984; see also, In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984.

The primary rejection alleged by the Examiner is based on the combination of Roth et al. in view of any one of Lu et al, Tango et al., or DePinho et al., and in further view of Tiemann. The Examiner alleges that Roth et al. disclose a variety of viral vectors that express p53, for the treatment of various cancers. Office Action at p. 3, ¶ 3. The Examiner acknowledges that Roth et al. do not teach methods for killing p53-positive cancer cells and do not suggest the use of a bicistronic vector encoding p53 and p14ARF under the control of a single promoter. Office Action at p. 4, ¶ 1.

With respect to the combination of p53 with p14ARF for the treatment of p53-positive cancer cells, the Examiner turns to any one of Lu et al., Tango et al., and/or DePinho. The Examiner alleges that each of these references teaches that p53 and p14ARF, encoded on separate vectors, may be used in combination to kill p53-positive cancer cells. Office Action at p. 4, ¶ 2 through p. 5, ¶ 1. The Examiner acknowledges that none of these references teaches the use of a bicistronic vector encoding p53 and p14ARF under the control of a single promoter. Office Action at p. 5, ¶ 2.

With respect to the combination of p53 and p14ARF into a bicistronic vector and under the control of a single promoter, the Examiner turns to Tiemann and/or Dirks et al. Office Action at p. 5, ¶ 3 through p. 6, ¶ 1. The Examiner alleges that Tiemann discloses a vector that conforms with the requirements of the claims. The Examiner relies on Dirks et al. for general teachings regarding the construction of bicistronic vectors of the type encompassed by the rejected claims.

Applicants respectfully submit that the cited prior art provides no motivation to combine or modify the teachings in a manner that results in the claimed invention, and further fails to provide a reasonable expectation of success in such a combination. Furthermore, Applicants have demonstrated that the claimed invention is surprisingly (as much as 40-fold) more effective than any comparable prior art method.

The cited prior art provides no motivation to combine.

As discussed in Applicants' Response of August 13, 2007, Lu et al. and Tango et al. do not motivate the combination of p53 and p14ARF onto a single vector, under the control of a single promoter, for killing p53-positive tumor cells. The experiments described in both Lu et al. and Tango et al. use different amounts of the p53 and p14ARF vectors for infection. As such, they would not be amenable to combination into a single vector. Specifically, Lu et al. performs only a single experiment in which p53-positive cells are simultaneously infected with p53 and p14ARF. In this experiment, the A549 cells are infected with 100 pfu/cell of Ad-p53 and 40 pfu/cell Ad-ARF. See, Lu et al. at p. 1308, Figure 3. Likewise, Tango et al performs similar experiments using the p53-positive TE8 cells. In each of Tango's experiments, TE8 cells were infected with 5 moi Ad-p53 and either 10, 30, 50, or 100 moi of Ad-ARF. See, Tango et al. at p. 1376, Figure 2, and p. 1377, Figure 3B. The only instance in which Tango et al. used the same amount of p53 and p14ARF was in experiments using p53-negative cell lines (e.g., H358 cells; see Figure 5C).

A skilled artisan would not be motivated to construct a vector encoding both p53 and p14ARF under the control of a single vector for killing p53-positive cancer cells in view of the experiments described by Lu et al. and Tango et al. Both of these references detail experiments in which the levels of p53 and p14ARF are individually controlled; a feature lost by their combination under control of a single promoter.

Newly cited DePinho does not provide any additional relevant teaching. The Examiner correctly characterizes DePinho as teaching that p14ARF tumor suppression is a p53-dependent event, and that the p14ARF effect is, at least partially mediated through MDM2 binding. MDM2 was known to inhibit the tumor-suppressing effects of p53, and p14ARF binding was demonstrated to block this inhibition. However, the Examiner has failed to demonstrate that the teachings of DePinho suggest that exogenous p53 expression should be combined with p14ARF in p53-positive cancer cells. Each of the experiments disclosed by DePinho involved the use of p53-negative cells. Thus, to the extent that DePinho suggests introducing p53 into cancer cells, such a treatment is only indicated in cells lacking functional p53. Furthermore, even if DePinho does suggest expressing exogenous p53 in p53-positive cells—which it does not—this teaching does not materially expand on the teachings of Lu et al. and Tango et al. discussed above.

In maintaining this aspect of the rejection, the Examiner states that it would have been obvious to insert the p14ARF sequence immediately downstream of the promoter in a single promoter-bicistronic system for the treatment of p53-positive cancer cells

> because the expression of exogenous p14ARF in already p53-positive cancer cells is more critical due at least to its ability to induce p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function.
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> Office Action at p. 9, ¶ 2.

The Examiner misapprehends the teachings of DePinho as they relate to Lu et al. and Tango et al. The question is not whether the prior art suggests expressing exogenous p53 in p53-positive tumor cells—Lu et al. and Tango et al. do—but whether it is obvious to combine p53 and p14ARF on a bicistronic vector for this purpose. The Examiner makes the statement that

such a combination is obvious, but provides no citation to the prior art and provides no rationale for the combination. Thus, this statement must be viewed merely as an impermissible hindsight reconstruction of Applicants' claimed invention from the prior art.

Taken together, nothing in Lu et al., Tango et al., and/or DePinho suggest the combination of p53 and p14ARF into a single vector, under the control of a single promoter, for killing p53-positive cancer cells. Only Lu et al. and Tango et al. specifically relate to p53-positive cancer cells, and each reference provides experiments in which the levels of p53 and p14ARF are individually controlled; an impossibility using Applicants' claimed method.

As a final source of motivation to combine, the Examiner turns to Tiemann and/or Dirks et al. The Examiner points out that Tiemann used p53/p14ARF vectors conforming to the rejected claims for the treatment of certain cancers. Office Action at p. 9, ¶ 1. However, as discusses in Applicants' Response of August 13, 2007, Tiemann only suggests using these vectors for killing p53-negative cancer cells (Hep3B cells). Here again, the prior art fails to suggest the use of a single vector encoding p53 and p14ARF under the control of a single promoter for killing p53-positive cancer cells.

Dirks et al. is of little import on the issue of motivation to combine. The Examiner cites Dirks et al. merely to demonstrate certain technical features relating to bicistronic vectors and for the suggestion that, under certain circumstances, the use of bicistronic vectors is advantageous. See, for example, Office Action at p. 8, ¶ 3. Nothing in Dirks et al. relates specifically to p53, p14ARF, and/or their utility for killing p53-positive cancer cells.

Here again, the Examiner has engaged in an impermissible hindsight reconstruction of Applicants' claimed invention by alleging the Tiemann and/or Dirks et al. motivate the use of Applicants' bicistronic vector for killing p53-positive cancer cells. In essence, the Examiner argues that the prior art technically could have performed Applicants' claimed invention. However, the Examiner has failed to identify where the prior art suggests that the artisan should

perform the claimed invention. For this reason alone, the *prima facie* case of obviousness is deficient and should be withdrawn.

Prior art provides no reasonable expectation of success

In addition to the lack of motivation to combine, Applicants submit that the cited prior art fails to provide a reasonable expectation of success for killing p53-positive cancer cells using a bicistronic vector encoding both a p53 and p14ARF under the control of a single promoter. The Examiner alleges that the skilled artisan would have reasonable expectation of success in light of the teachings of Roth et al. in view of any one of Lu et al., Tango et al., or DePinho, and Tiemann and Dirks et al. Office Action mailed 1/29/08 at p.7, ¶ 2. Applicants respectfully disagree and submit that the prior art provides no expectation of success in using the claimed bicistronic vectors for killing p53-positive cancer cells.

None of Roth et al., Lu et al., Tango et al., and DePinho teaches a bicistronic vector encoding p53 and p14ARF. At most, these references teach that the combination of p53 and p14ARF may be successful in killing p53 cancer cells when administered on separate vectors. The Examiner implies that the artisan has an expectation of successfully using p53 and p14ARF on a single vector and under the control of a single promoter based on the teachings of Tiemann and/or Dirks et al.

The teachings of Tiemann are irrelevant because Tiemann is only concerned with treating p53-negative cancer cells. Nothing in Tiemann indicates that the bicistronic vector could be successfully applied to p53-positive cancer cells. Any implication by the Examiner otherwise is mere speculation and hindsight reconstruction based on Applicants' disclosure.

Dirks et al. is also irrelevant to the expectation of success with regard to the use of p53/p14ARF bicistronic vectors for killing p53-positive cancer cells. Dirks et al. discloses the preparation of multicistronic vectors that result in the equimolar expression of the encoded polypeptides. Dirk provides limited examples of genes contained in the cistrons, but none of

these genes include p53 or p14ARF. Dirks et al. at column 7, lines 2-9. Furthermore, nothing in Dirk et al. relates to killing p53-positive cancer cells. Thus, it will be erroneous to assume that the general teachings of Dirks et al. will be applicable to the specific case of a bicistronic construct of p53 and p14ARF under the control of a single promoter as asserted by the Examiner.

When taken together, the prior art relied upon by the Examiner fails to provide a motivation to use a bicistronic p53/p14ARF vector for killing p53-positive cancer cells and, based on the art, the artisan has no reasonable expectation of success. The art clearly demonstrates a perceived need for independent regulation of the infective levels of each construct, thus negating the possibility of their combination into a single vector. Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness. This rejection is traversed and should be withdrawn.

Applicants demonstrate surprising and unexpected results using the bicistronic construct for the treatment of p53-positive cancer cells

Even accepting, *arguendo*, that a *prima facie* case of obviousness has been made, it may be rebutted by evidence of an unexpected result. M.P.E.P. § 2144.08(II)(B) ("Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art.").

In the Declaration by Dr. Gjerset, submitted October 31, 2007, Applicants provide unequivocal evidence that the claimed method yields unexpectedly improved properties relative to what is predicted by the prior art. In this Declaration, Dr. Gjerset provides recent experimental results directly comparing the relative effectiveness of the single promoter p53/p14ARF bicistronic vector with a dual vector system. Specifically, Dr. Gjerset compared the killing effect of a bicistronic p53/p14ARF vector that falls within the scope of the rejected claims, with the killing effect of simultaneous infection of a p53 vector and p14ARF vector. In order to control for possible differences in the level of infection and/or expression of individual p53 and p14ARF vectors in the dual vector system, relatively high vector levels were used. These levels ensured

that virtually all of the test cells received and expressed both vectors. Gjerset Declaration at ¶ 7-11.

Dr. Gjerset demonstrated the unexpected finding that 10 moi of the bicistronic construct of p53 and p14ARF resulted in greater p53-positive cancer cell growth suppression than 200 moi of each individual vector used in combination. Gjerset Declaration at ¶ 14. Interpolation of these results led Dr. Gjerset to conclude that approximately 5 moi of the bicistronic vector had equivalent efficacy to the combination of about 200 moi of each individual vector. Gjerset Declaration at ¶ 14. This represents a 40-fold increase in efficacy for the bicistronic vector compared to what is predicted by a combination of the individual vectors. Gjerset Declaration at ¶ 14.

The Examiner while analyzing the results of Dr. Gjerset made conclusory statements without providing any support for his assertion. The Examiner has alleged that the calculations to arrive at the moi of 10 that yields virtually 100% cells in the dual vector system to receive both vectors and the 40-fold increase in efficacy for the bicistronic vector are flawed because the calculations did not take into account: a) dominance of one vector over the other in copy number as well as expression in transfected cells; b) cellular uptake of at least two different vectors in a stable manner; c) mRNA encoding p53 and p14ARF resulted from two vector constructs may not possess the same stability and translation efficiency; d) cells already transfected with one vector may not have the same probability to be further transfected with another vector (same or different). The Examiner concludes that these possible technical differences could skew the data in favor of the bicistronic construct.

The Examiner's analysis of Dr. Gjerset's results is flawed for several reasons. While performing the comparative study, Dr. Gjerset used the same adenoviral vector for bicistronic and monocistronic constructs. Thus, the probability of cells to be infected with any adenoviral vectors either monocistronic or bicistronic construct is same, not different as asserted by the Examiner. The cellular uptake of two adenoviral vector constructs encoding p53 and p14ARF will be same and not different. The p53 and p14ARF mRNA transcribed from the adenoviral

vector were under the control of the same CMV promoter. Thus, without providing any evidence to the contrary the Examiner made conclusory statement that the stability and translational efficiency of the two mRNA will be different.

Applicants respectfully submit that the Examiner has provided no evidence to substantiate any of the concerns raised, rendering these concerns an improper basis to entirely dismiss Dr. Gjerset's data. Applicants stress that the Examiner's allegations are based solely on an incomplete analysis of the 10 moi condition without regard for the entirety of the data set. Furthermore, Dr. Gjerset's experiments are not limited to the use of 10 moi of each vector. Dr. Gjerset used as much as 200 moi of each vector; 20-fold higher than the 10 moi with which the Examiner takes issue. This 20-fold excess would be expected to overcome any minor differences raised by the Examiner. The Examiner has not addressed the consistency of Dr. Gjerset's data over such a wide moi range.

Applicants respectfully submit that the Examiner has incorrectly dismissed the data presented by Dr. Gjerset. This data clearly and unequivocally demonstrates that Applicants' claimed method is surprisingly more effective for killing p53-positive cancer cells than would be predicted by the prior art. Accordingly, even if the Examiner has made a prima facie case of obviousness against the rejected claims (which Applicants urge has not been done), this unexpected result is sufficient to rebut the rejection.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to

Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741

Respectfully submitted,

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